



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,328	02/12/2002	Jeff Steven Grotelueschen Hall	FORS-06930	5712

23535 7590 12/27/2006  
MEDLEN & CARROLL, LLP  
101 HOWARD STREET  
SUITE 350  
SAN FRANCISCO, CA 94105

EXAMINER
----------

SITTON, JEHANNE SOUAYA

ART UNIT	PAPER NUMBER
----------	--------------

1634

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/074,328	<b>Applicant(s)</b> GROTELUESCHEN HALL ET AL.	
	<b>Examiner</b> Jehanne S. Sitton	<b>Art Unit</b> 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 101,104-106 and 111-125 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 101,104-106 and 111-125 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>See Continuation Sheet</u> .           |

Continuation of Attachment(s) 6). Other: New England Biolabs, Heat Inactivation of Restriction Endonucleases.

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.
2. Currently, claims 101, 104-106 and 111-125 are pending in the instant office action. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non-FINAL.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Maintained Rejections***

#### ***Claim Rejections - 35 USC § 102***

4. Claims 101, 104, 111-117, and 123-125 rejected under 35 U.S.C. 102(b) as being anticipated by Harrington I (Harrington et al.; The EMBO Journal, vol 13, pp 1235-1246, 1994).

Art Unit: 1634

With regard to claim 101, Harrington I teaches a set of oligonucleotides as follows: 1) a target nucleic acid HJ41 (Figure 8a, lanes 3-5) (claims 114-115, it is noted that the claims do not require that the first and second target be different, therefore more than one copy of the target nucleic acid can be considered first, second, third, etc, target nucleic acids. Alternatively, any of the other nucleic acids taught by Harrington I - see page 1245, col 1 "oligonucleotides"- can be considered a second "target" nucleic acid, as claim 115 does not provide any structural limitations with regard to the "second target nucleic acid"), 2) a first oligonucleotide HJ40 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group; with regard to claim 125, HJ40 comprises an uncleavable region) alternatively, HJ42 can be considered a first oligonucleotide as it comprises a portion completely complementary a first region of a target nucleic acid; 3) a second oligonucleotide HJ39, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. With regard to claim 104, Harrington I teaches administering such oligonucleotides to a gel, which is considered a solid support. With regard to claim 112, Harrington I teaches a buffer solution (see page 1245). With regard to claim 113, Harrington I teaches a third oligonucleotide HJ49, complementary to a third

Art Unit: 1634

region of said target nucleic acid upstream of said first region of said target nucleic acid. It is noted that the term “providing” in claim 113 has been given no weight as the claims are drawn to products and not to methods requiring a step such as “providing”. With regard to claim 116, the claim sets forth no structural limitations for “linker”. Therefore the term has been given it’s broadest reasonable meaning which encompasses the sugar group of the nucleotide. With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, molecule HJ42 comprises a label at it’s 5’ end (claim 123). With regard to claim 124, either HJ42 or HJ40 comprise an uncleavable region.

5. Claims 101, 104, 111-117, and 123-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Harrington II (Harrington et al; Journal of Biological Chemistry, vol. 270, pp 4503-4508, 1995).

With regard to claim 101, Harrington II teaches a set of oligonucleotides as follows: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15) (claims 114-115, it is noted that the claims do not require that the first and second target be different, therefore more than one copy of the target nucleic acid can be considered first, second, third, etc, target nucleic acids. Alternatively, any of the other nucleic acids taught by Harrington - see page 4503, col 2 “oligonucleotides”- can be considered a second “target” nucleic acid, as claim 115 does not provide any structural limitations with regard to the “second target nucleic acid”), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a “charged adduct” is broadly interpreted to encompass a single nucleotide or charged phosphate group; with regard to claim 125, HJ46 comprises an uncleavable region); 3) a second

Art Unit: 1634

oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. With regard to claim 104, Harrington II teaches administering such oligonucleotides to a gel, which is considered a solid support. With regard to claim 112, Harrington II teaches a buffer solution (see page 4504). With regard to claim 116, the claim sets forth no structural limitations for "linker". Therefore the term has been given it's broadest reasonable meaning which encompasses the sugar group of the nucleotide. With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, molecule HJ46 comprises a label at it's 5' end (claim 123). With regard to claim 124, HJ46 comprises an uncleavable region as it comprises regions not cleaved in the reaction.

### ***Response to Arguments***

6. The response traverses both rejection under 35 USC 102(b) over Harrington I, and in the alternative, Harrington II. The response asserts the term "thermostable" is defined at page 32 lines 16-18 of the specification, and that neither Harrington I or II teach or recite a thermostable 5' nuclease "ie, a 5' nuclease that is functional or active at about 55°C or higher", but rather teach a nuclease used at 30°C, not one that is functional or active at "about" 55°C or higher. The

Art Unit: 1634

response further asserts that neither Harrington I or II teach or suggest that the disclosed enzymes have any stability or activity at or above "about" 55°C. This argument has been thoroughly reviewed but was found unpersuasive. Firstly, it is noted that the specification does not define the term to be limited to any specific level or amount of catalytic activity or stability. Further, the recitation of "about" 55°C is not clearly defined, such that the lower limit encompassed by "about 55°C" for catalytic activity is not defined. The FEN-1 endonucleases taught by both Harrington I and Harrington II are homologous to FEN-1 endonucleases which have been isolated from thermophilic organisms, which have catalytic activity at the recited temperature. Additionally, as taught by New England Biolabs, the majority of restriction endonucleases require temperatures of 65°C or higher for 20 minutes for heat inactivation. Accordingly, the PTO has basis for believing that the FEN-1 endonucleases taught by Harrington I and II, have some level of catalytic activity, albeit not optimal, at "about" 55°C. As stated in the MPEP:

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

### ***Claim Rejections - 35 USC § 103***

7. Claims 105 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington I in view of Dahlberg (WO 94/29482).

Harrington I teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini or 5' termini and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington I teaches among other



Art Unit: 1634

reagents: 1) a target nucleic acid HJ41 (Figure 8a, lanes 3-5), 2) a first oligonucleotide HJ40 comprising a charged adduct and a portion completely complementary to the target (a “charged adduct” is broadly interpreted to encompass a single nucleotide or charged phosphate group) alternatively, HJ42 can be considered a first oligonucleotide as it comprises a portion completely complementary a first region of a target nucleic acid; 3) a second oligonucleotide HJ39, comprising a 3’ portion and a 5’ portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5’ nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington I does not teach a method wherein the first oligonucleotide (claims 105) or the second oligonucleotide (claim 106) is attached to a solid support, however Dahlberg teaches a method wherein cleavage structures as taught by Harrington I are subjected to cleavage reactions with 5’ nucleases, as taught by Harrington I wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleavage structures are released from the immobilized structure for further analysis. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to immobilize the first or second oligonucleotide taught by Harrington I to a solid support as taught by Dahlberg. The ordinary artisan would have been motivated to attach either the first or second

Art Unit: 1634

oligonucleotide in the cleavage structures of Harrington I to a solid support as taught by Dahlberg for ease of cleavage detection as taught by Dahlberg.

8. Claims 105 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington II in view of Dahlberg.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini, 5' termini, or both, and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington II teaches among other reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington II does not teach assays wherein the first oligonucleotide (claims 105) or the second oligonucleotide (claim 106) is attached to a solid support, however Dahlberg teaches a method wherein cleavage structures as taught by Harrington are subjected to cleavage reactions with 5' nucleases, as taught by Harrington II

Art Unit: 1634

wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleavage structures are released from the immobilized structure for further analysis. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to immobilize the first or second oligonucleotide taught by Harrington II to a solid support as taught by Dahlberg. The ordinary artisan would have been motivated to attach either the first or second oligonucleotide in the cleavage structures of Harrington II to a solid support as taught by Dahlberg for ease of cleavage detection as taught by Dahlberg.

9. Claims 105-106, 118-119 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington I in view of Urdea.

Harrington I teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini or 5' termini and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington I teaches among other reagents, 1) a target nucleic acid HJ41 (Figure 8a, lanes 3-5), 2) a first oligonucleotide HJ40 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group) alternatively, HJ42 can be considered a first oligonucleotide as it comprises a portion completely complementary a first region of a target nucleic acid; 3) a second oligonucleotide HJ39, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence

Art Unit: 1634

wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington I does not teach a method wherein the first oligonucleotide (claim 105) or the second oligonucleotide (claim 106) is attached to a solid support or wherein the first oligonucleotide comprising a charged adduct comprises a detectable molecule which is fluorescein (claims 118-119) or wherein the charged adduct comprises at least one amino modified base (claim 122), however Urdea teaches detection of cleaved labeled nucleic acid molecules attaches to a solid support wherein separation of the label from the solid support is detected and indicates cleavage (col. 8, lines 47-55, Figures 2 and 3). Urdea further teaches labeling the nucleic acid with fluorescein which is incorporated on an amino modified base such as cytosine or uracil (col. 9, lines 45-50). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the first oligonucleotide of Harrington I with fluorescein on an amino modified base, and to attach either the first oligonucleotide or the second oligonucleotide on a solid support as taught by Urdea because Urdea teaches detection of cleaved nucleic acids by separation of a labeled nucleic acid from a solid support and teaches labels such as fluorescein on an amino modified base can be used. The ordinary artisan would have been motivated to improve the method of Harrington I with the use of the solid support and labeled nucleic acid as taught by Urdea for ease of detection as taught by Urdea and to minimize the use of radioactively labels.

Art Unit: 1634

10. Claims 105-106, 118-119, and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington II in view of Urdea.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini, 5' termini, or both, and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington II teaches among other reagents: 1) a target nucleic acid A14 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington II does not teach a method wherein the first oligonucleotide (claims 105) or the second oligonucleotide (claim 106) is attached to a solid support or wherein the first oligonucleotide comprising a charged adduct comprises a detectable molecule which is fluorescein (claims 118-119) or wherein the charged adduct comprises at least one amino modified base (claim 122), however Urdea teaches detection of cleaved labeled nucleic acid molecules attaches to a solid support wherein separation of the label from the solid support is detected and indicates cleavage (col. 8, lines 47-55, Figures 2 and

Art Unit: 1634

3). Urdea further teaches labeling the nucleic acid with fluorescein which is incorporated on an amino modified base such as cytosine or uracil (col. 9, lines 45-50). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the first oligonucleotide of Harrington II with fluorescein on an amino modified base, and to attach either the first oligonucleotide or the second oligonucleotide on a solid support as taught by Urdea because Urdea teaches detection of cleaved nucleic acids by separation of a labeled nucleic acid from a solid support and teaches labels such as fluorescein on an amino modified base can be used. The ordinary artisan would have been motivated to improve the method of Harrington II with the use of the solid support and labeled nucleic acid as taught by Urdea for ease of detection as taught by Urdea and to minimize the use of radioactive labels.

11. Claims 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington in view of Corey.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini or 5' termini and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington teaches among other reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic

Art Unit: 1634

activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington does not teach wherein the first oligonucleotide comprises a charged adduct which comprises at least one amino acid (claim 120), wherein the amino acid is lysine, arginine, aspartate, or glutamate (claim 121), however Corey teaches that the addition of positively charged peptides in a nucleic acid sequence accelerates and enhances hybridization of that nucleic acid sequence, and that peptides containing as few as four lysines increased  $K_a$  by 5 fold. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the assays of Harrington with the use of positively charged peptides taught by Corey in the oligonucleotide structures of Harrington, including the first oligonucleotide. The ordinary artisan would have been motivated to modify the oligonucleotides of Harrington for the purpose of accelerating hybridization, as taught by Corey, in the assays of Harrington, and thus enhancing the assays of Harrington.

12. Claims 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington II in view of Corey.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini, 5' termini, or both, and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington II teaches among other

Art Unit: 1634

reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington II does not teach wherein the first oligonucleotide comprises a charged adduct which comprises at least one amino acid (claim 120), wherein the amino acid is lysine, arginine, aspartate, or glutamate (claim 121), however Corey teaches that the addition of positively charged peptides in a nucleic acid sequence accelerates and enhances hybridization of that nucleic acid sequence, and that peptides containing as few as four lysines increased  $K_a$  by 5 fold. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the assays of Harrington II with the use of positively charged peptides taught by Corey in the oligonucleotide structures of Harrington II, including the first oligonucleotide. The ordinary artisan would have been motivated to modify the oligonucleotides of Harrington II for the purpose of accelerating hybridization, as taught by Corey, in the assays of Harrington II, and thus enhancing the assays of Harrington II.



### ***Response to Arguments***

13. The response traverses all rejections under 35 USC 103, which utilize Harrington I or II as primary reference, under the same grounds. The response asserts that neither Harrington I or II teach the combination of "first and second oligonucleotides that comprise defined regions of complementarity to a target nucleic acid such that they form an overlapped structure when annealed to the target nucleic acid; and a [2] thermostable 5' nuclease lacking synthetic activity" and that none of the secondary references of Dahlberg, Corey, or Urdea overcome these deficiencies. These arguments have been thoroughly reviewed but were found unpersuasive for the reasons made of record at section 6 above.

### ***Double Patenting***

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 101, 104-106, 111-120 and 122-125 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/031,487. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of

Art Unit: 1634

the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the HCV 5' UTR and its 3' portion does not. As defined by the specification of the '487 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '487 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No.

Art Unit: 1634

11/031,487 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the HCV 5' UTR and its 3' portion does not. As defined by the specification of the '487 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '487 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '487 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '487 application.

This is a provisional obviousness-type double patenting rejection.

Art Unit: 1634

17. Claims 101, 104-106, 111-120, and 122-125 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '408 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

Art Unit: 1634

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '408

Art Unit: 1634

application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '408 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '408 application

This is a provisional obviousness-type double patenting rejection.

19. The response provides no arguments with regard to the obviousness type double patenting rejections set forth above. Accordingly, the rejections are maintained for the reasons made of record above and in previous office actions.

### ***Conclusion***

20. No claims are allowable over the cited prior art.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Art Unit: 1634

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Jehanne Sitton  
Primary Examiner  
Art Unit 1634

~~12/1/06~~

12/21/06